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How to Develop Treatments for Biologically Heterogeneous "Diseases"

Richard M. Simon

The standard paradigm for the design of phase III clinical trials is not suitable for evaluation of molecularly targeted treatments in biologically heterogeneous groups of patients. Here, we comment on alternative clinical trial designs and propose a prospective discovery/evaluation framework for using tumor genomics in the design of phase III trials. Clin Cancer Res; 18(15); 4001–3. ©2012 AACR.

In this issue of Clinical Cancer Research, Redman and colleagues (1) describe the design of a new phase III clinical trial of cetuximab in non–small cell lung cancer (NSCLC). Clinical trials are generally designed to test a single null hypothesis for all randomized patients with eligibility defined by histology, stage, and amount of previous treatment. Rejection of the null hypothesis can lead to regulatory approval of the drug for patients who satisfy the eligibility requirements of the trial. In many cases, this paradigm no longer provides a scientifically sound or economically sustainable basis for phase III clinical trials; the paradigm would not be scientifically sound because most histologic diagnoses are heterogeneous in oncogenesis and pathogenesis and sensitive to molecularly targeted therapy, and it would not be economically sustainable because approving drugs based on very small average treatment effects for broad populations creates a heavy economic burden (2).

We are in search of a new paradigm for therapeutic development in oncology (3). Although there is uncertainty on what this new paradigm should be, the inadequacies of the existing paradigm are illustrated by the development of cetuximab for patients with NSCLC. There is substantial evidence that epidermal growth factor receptor (EGFR) signaling is of importance for some NSCLC tumors (4), and 2 large phase III trials have been conducted. The FLEX trial reported a statistically significant 1.2-month increase in median survival for the cetuximab arm. BMS 099 reported a nonsignificant 1.3-month increase in median survival for the cetuximab arm and a 0.5-month improvement in median progression-free survival (PFS). Neither trial selected patients or even evaluated tumors for genomic alterations in EGFR. These clinical trials are representative of the current paradigm in which large clinical trials are conducted without detailed prospective biologic characterization of the tumors and without prospective archiving of tumor specimens on all patients to enable discovery.

Redman and colleagues provide a nice analysis of the relative merits of 4 design options that they considered for the design of a new phase III trial to evaluate EGFR amplification as a predictive biomarker for benefit from cetuximab. The first option is to repeat the “all comers” design used in the 2 previous phase III trials in which evaluation of cetuximab in the subsets based on EGFR amplification is only exploratory. “Exploratory” generally means that none of the 5% type I error for the trial is reserved for that subset analysis, the trial may not be sized for the subset analysis, and submission of tumor specimens for the analysis is not a condition for enrolment. One clearly does not need another trial of that type.

The second design option considered by Redman and colleagues is the “strategy design,” in which patients are randomized to either have their tumor tested for EGFR amplification or not. If not, they receive standard-of-care chemotherapy. If tested, they would receive cetuximab-augmented chemotherapy only if their tumor were found to be EGFR amplified. Strategy designs are generally a very poor choice (5). They require an enormous sample size because many patients receive the same treatment regardless of the arm to which they are randomized.

The third design option is the “enrichment design,” in which only patients with EGFR-amplified tumors would be eligible (6). Enrichment can be very efficient with regard to minimizing the required number of randomized patients and the cost of the trial. Although it seems clear from the previous phase III trials that the patients without EGFR amplification as a group do not benefit meaningfully from cetuximab, including such patients would enable reanalysis of the results of the trial with regard to candidate biomarkers discovered later, using the “prospective-retrospective” design (5).

The multiple hypotheses designs considered by Redman and colleagues were described previously by Simon (7) as a single design in which the 5% type I error (α) of the clinical trial is partitioned among the various hypotheses that are tested. How the 5% alpha is split up can depend on the degree of confidence one has in the marker or it can be...
optimized to achieve the desired power for each hypothesis

Redman and colleagues selected the multiple hypothesis
design for their trial with their hypotheses of interest being
the null hypothesis of no benefit for all randomized patients
and the null hypothesis of no benefit for the EGFR-ampli-
fied patients. However, the first null hypothesis has already
been tested in 2 previous large phase III trials. A second
concern is the large number of patients without EGFR
amplification likely to be enrolled. Karuri and Simon (8)
recently published a Bayesian design to better protect test-
negative patients. The study-wise type I error is protected,
but it monitors for futility in test-negative patients more
aggressively than the design proposed by Redman and
colleagues.

An additional design option that should be considered
for many phase III trials is the “Adaptive Signature Design”
(9) illustrated in Fig. 1. It is a discovery design based on
the admission that we do not know enough about the factors
that influence response to cetuximab in NSCLCs and should
try to prospectively ensure that the phase III trial extends
that knowledge. The previous phase III clinical trials already
conducted for cetuximab indicate that the improvement in
median survival for EGFR-amplified patients is unlikely to
exceed 4 months. The proposed trial is sized to detect an
increase in median PFS of less than 2 months in EGFR-
amplified patients. Is it worthwhile to detect such small
effects? We need to better understand what aspects of the
genetic background of lung tumors determine whether a
patient is likely to benefit from cetuximab treatment. The
Adaptive Signature Design is structured to do discovery
based on a more comprehensive genomic characterization.
At the time of final analysis, the patients are partitioned into
a training set and a validation set. The genomic character-
ization and outcome data in the training set are analyzed to
train a multivariate classifier that identifies the genomic
characteristics of patients who benefit from cetuximab. That
classifier is tested on the validation set. This design can also
be implemented sequentially in time as described by Sher
and colleagues (10), and the statistical power of the
approach can be substantially enhanced by using cross-
validation rather than sample splitting as described by
Freidlin and colleagues (11) and by Simon (3).

Redman and colleagues have provided an analysis that
will be useful for planning clinical trials of treatments and
prespecified predictive biomarkers. An important aspect of
the design of many such phase III clinical trials, however, is

Figure 1. Schematic for the
Adaptive Signature Design (9). The
tumors of all randomized
patients are molecularly
characterized with regard to a
trial-specific set of discovery
features to be evaluated.
Eligibility is not restricted by
the molecular characterization. At
final analysis, patients are
randomly partitioned into a
training set and validation set. A
binary classifier is trained to
identify patients for whom the
difference in outcomes
between the treatment arms is
maximum. The binary classifier
is tested on the validation set.
The design uses a predictive
classifier discovery and
evaluation framework, not a
multiple hypothesis testing
framework. The trial is sized for
discovery and validation as
illustrated by Sher and
colleagues (10).
to ensure that tumor samples or tumor DNA are preserved for all randomized patients for future analysis. Our understanding of the interactions among signaling pathways is still rudimentary, and the discovery objective of phase III clinical trials warrants increased emphasis.

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No potential conflicts of interests were disclosed.

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